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10/540,854	09/01/2006	Nicole Francine Rouquet	065691-0396	2346

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EXAMINER	
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1636	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/540,854	ROUQUET ET AL.	
	Examiner	Art Unit	
	CATHERINE HIBBERT	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 April 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20* is/are pending in the application.

4a) Of the above claim(s) *10,11 and 13-20* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9 and 12* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *27 June 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☒ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *6/27/2005; 3/6/208*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This is the First Office Action on the Merits of US Application 10/540,854, filed 1 September 2006, which is a National Stage Entry of PCT/FR2003/003897, filed 24 December 2003, which claims priority from French patent application FR 02/16785, filed 27 December 2002. Claims 1-20 are pending. Claims 10-11 and 13-20 are withdrawn herein to non-elected subject matter. Claims 1-9 and 12 are under examination in this action.

Election/Restrictions

Applicant's election with traverse of Group I (Claims 1-12), and of the species of Claim 12 (from among the species Claims 10, 11 or 12), in the reply filed on 24 April 2009 is acknowledged. The traversal is on the ground(s) that Applicants argue that "[t]he Office erred in mischaracterizing the technical feature common to Groups I-II", stating that the technical feature common to Groups I-II is "'the particles obtained by the method of claim 1'". Further, Applicants argue that "[t]hese particles result from the claim 1 'method for attaching DNA in plasmid form to the surface of calcium phosphate ceramic or powder'". In addition, Applicants argue that the "Office erred in failing to indicate where Okazaki discloses particles resulting from a 'method for attaching DNA in plasmid form to the surface of calcium phosphate ceramic or powder'" and further state that "[b]ecause of these distinct and specific errors, the restriction requirement is improper and should be withdrawn".

Applicants arguments have been carefully considered but are respectfully not found persuasive for reasons already of record and because Claim 13 recites "[a] calcium phosphate ceramic and powder which can be obtained from the method as claimed in claim 1, wherein epitaxial carbonated apatite growth at the surface of the calcium phosphate ceramic and powder

under nondenaturing conditions is supported". Therefore, the only technical feature that is required of Claim 13, as written, is a calcium phosphate ceramic and powder. Therefore the only technical feature that is common to Groups I and II is a calcium phosphate ceramic and powder, which is not novel over Okazaki et al (2001; of record) for reasons already of record in the previous office action.

In addition, Applicant traverses the election of species requirement, stating that

> Applicants traverse the election of species requirement by distinctly and specifically pointing out the following errors. The Office erred in failing to set forth any applicable legal standard to which the facts were applied. The Office then merely identifies the difference between the species ("The species are independent or distinct because they are methods of materially different design using cultured cells in monolayers versus cultured tissue fragments, versus in vivo cells in a tissue or organ."). In doing so, the Office essentially stated that "the species are independent or distinct because they are different." This is not a proper basis for requiring an election of species under any relevant legal standard. Because of these distinct and specific errors, the election of species requirement is improper and should be withdrawn.

This is not found persuasive for reasons already of record and because as stated in the previous action, the species are independent or distinct because they are methods of materially different design using cultured cells in monolayers versus cultured tissue fragments, versus in vivo cells in a tissue or organ.

The requirement is still deemed proper and is therefore made FINAL.

Claims 10-11 and 13-20 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected subject matter, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 24 April 2009.

It is noted that Applicants states in the reply filed on 24 April 2009 that Claims 1-9 are generic to the elected species.

Information Disclosure Statement

It is noted that the information disclosure statement (IDS) submitted on 3/6/2008 is the same IDS filed 6/27/2005 except that the date for the A6 (Paul et al) reference is present and thus the A6 (Paul et al) reference has been considered by the examiner.

The information disclosure statement filed 6/27/2005 fails to comply with the provisions of 37 CFR 1.97, 1.98 and MPEP § 609 because the reference A6 (Paul et al) is missing a date. It has been placed in the application file, but the information referred to therein that has been lined through has not been considered as to the merits. Applicant is advised that the date of any re-submission of any item of information contained in this information disclosure statement or the submission of any missing element(s) will be the date of submission for purposes of determining compliance with the requirements based on the time of filing the statement, including all certification requirements for statements under 37 CFR 1.97(e). See MPEP § 609.05(a).

Oath/Declaration

The oath or declaration and the ADS are objected to for the following reason. See MPEP §§ 602.01 and 602.02. The oath or declaration and the ADS are objected to because they contain different filing dates. It is incumbent upon Applicant to correct this discrepancy as part of a complete response to this Office Action.

Specification

It is noted that in the instant specification, the section for the Brief Description of the Drawings is missing but the Figures 1 and 2 are referred to under Example 3. The following guidelines illustrate the preferred layout for the specification of a utility application. These guidelines are suggested for the applicant's use.

Arrangement of the Specification

As provided in 37 CFR 1.77(b), the specification of a utility application should include the following sections in order. Each of the lettered items should appear in upper case, without underlining or bold type, as a section heading. If no text follows the section heading, the phrase "Not Applicable" should follow the section heading:

(a) TITLE OF THE INVENTION.
(b) CROSS-REFERENCE TO RELATED APPLICATIONS.
(c) STATEMENT REGARDING FEDERALLY SPONSORED RESEARCH OR DEVELOPMENT.
(d) THE NAMES OF THE PARTIES TO A JOINT RESEARCH AGREEMENT.
(e) INCORPORATION-BY-REFERENCE OF MATERIAL SUBMITTED ON A COMPACT DISC.
(f) BACKGROUND OF THE INVENTION.
    (1) Field of the Invention.
    (2) Description of Related Art including information disclosed under 37 CFR 1.97 and 1.98.
(g) BRIEF SUMMARY OF THE INVENTION.
(h) BRIEF DESCRIPTION OF THE SEVERAL VIEWS OF THE DRAWING(S).
(i) DETAILED DESCRIPTION OF THE INVENTION.
(j) CLAIM OR CLAIMS (commencing on a separate sheet).
(k) ABSTRACT OF THE DISCLOSURE (commencing on a separate sheet).
(l) SEQUENCE LISTING (See MPEP § 2424 and 37 CFR 1.821-1.825. A "Sequence Listing" is required on paper if the application discloses a nucleotide or amino acid sequence as defined in 37 CFR 1.821(a) and if the required "Sequence Listing" is not submitted as an electronic document on compact disc).

Claim Objections

Claim 1 is objected to because of the following informalities: Claim 1 contains a grammatical error which requires a correction such as removal of the term "c)" in line 8 or addition of a conjunctive term such as "and" in line 8 just before the term "c)".

Additionally, Claim 1 contains a grammatical error regarding the use of the plural of "particles" with the singular term "its" in the phrase "producing calcium phosphate particles containing DNA molecules attached to its surface" in lines 8-9.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 3, 6, 7 and 9 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Regarding Claims 3 and 6, a broad range or limitation together with a narrow range or limitation that falls within the broad range or limitation (in the same claim) is considered indefinite, since the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. See MPEP § 2173.05(c). Note the explanation given by the Board of Patent Appeals and Interferences in *Ex parte Wu*, 10 USPQ2d 2031, 2033 (Bd. Pat. App. & Inter. 1989), as to where broad language is followed by "such as" and then narrow language. The Board stated that this can render a claim indefinite by raising a question or doubt as to whether the feature introduced by such language is (a) merely exemplary of the remainder of the claim, and therefore not required, or (b) a required feature of the claims. Note also, for example, the decisions of *Ex parte Steigewald*, 131 USPQ 74 (Bd. App. 1961); *Ex parte Hall*, 83 USPQ 38 (Bd. App. 1948); and *Ex parte Hasche*, 86 USPQ 481 (Bd. App. 1949). In the present instance, claims 3 and 6 recite the broad recitation "15 to 50°C ", and the claims also recite "preferably about 37°C" which is the narrower statement of the range/limitation.

Claim 7 recites the limitation "the extracellular fluids" in 3. There is insufficient antecedent basis for this limitation in the claim because there is not prior reference to any extracellular fluids.

It is noted that Claim 9 recites "[t]he method as claimed in claim 7 to attach DNA under physiological pH conditions to calcium phosphate particles". Therefore, Claim 9 does not include any additional active method steps but adds limitations only to the preamble of the claim. Therefore, it is unclear what is required of one of ordinary skill in the art to perform the claimed method to achieve the intended outcome of the preamble.

Additionally, Claim 9 is indefinite insofar as it depends from Claim 7.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-9 and 12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Troczynsky et al in "Biofunctional Hydroxyapatite Coatings and Microspheres for In-Situ Drug Encapsulation" (WO 02/085330, published 31 October 2002; made of record in the IDS).

Claim 1 is drawn to a method for attaching DNA in plasmid form to the surface of calcium phosphate ceramic or powder, comprising a step (a) consisting of a hydration of the calcium phosphate powder or calcium phosphate ceramic in a phosphate buffer solution not saturated with calcium and phosphate and a step (b) consisting of an immersion of the products obtained in step (a) in a phosphate buffer solution not saturated with calcium and phosphate containing a single- or double-stranded DNA for periods varying from a few minutes to several hours, (c) producing calcium phosphate particles containing DNA molecules attached to its surface.

Troczynsky et al teach a hydration of the calcium phosphate powder or calcium phosphate ceramic in a phosphate buffer solution not saturated with calcium and phosphate (step a), stating: "The microspheres of the precursors can be exposed to a water-based solution of phosphate ions and incubated in a humid environment at a temperature of 20-50°C to promote dissolution of the precursors and precipitation of calcium phosphate phase" (e.g. paragraph bridging pages 10-11 and page 13, lines 1-5), and teach an immersion of the products obtained in step (a) in a phosphate buffer solution not saturated with calcium and phosphate containing a

single- or double-stranded DNA for periods varying from a few minutes to several hours (step b) (e.g. page 13, lines 5-9) thus producing calcium phosphate particles containing DNA molecules attached to the particles (step c) (e.g. page 13, lines 9-11) stating that: "[a] crystalline hydroxyapatite powder can be added to the precursors slurry to promote crystallization of hydroxyapatite calcium phosphate phase during the incubation period" and continue "[a] therapeutically active material can be added to the precursors slurry for encapsulation during crystallization of the hydroxyapatite calcium phosphate phase during the incubation period", further stating that "[t]he therapeutically active material can be a drug, a protein, a gene or DNA" (page 10, lines 21-26).

Claim 3 specifies within Claim 1 that the immersion is carried out for at least 1, 5, 10 or 30 minutes up to about 12, 24 or 48 hours at a temperature ranging from 15 to 50°C., preferably about 37°C.

Regarding Claim 3, Troczynsky et al teach the process of making the calcium phosphate (in particular hydroxyapatite) microspheres (particles) designed specifically for gene therapy through gene/DNA/plasmid delivery occurs at room-temperature (i.e. about 25°C) and teach the drug material (e.g. DNA) is exposed to water-based solution of sodium phosphate and placed in an incubator at 37°C, 100% relative humidity, for up to 24 h. (e.g. page 12, lines 21-23).

Claim 4 specifies within Claim 1 that the calcium phosphate particles are kept immersed in a culture medium of the cell culture media type. Claim 5 specifies within Claim 4 that the calcium phosphate particles are immersed for about a few minutes to a few days. Claim 6 specifies within Claim 4 that the calcium phosphate particles are immersed at a temperature ranging from 15 to 50°C., preferably about 37°C. Claim 7 specifies within Claim 1 that step b)

is carried out by means of a medium simulating the extracellular fluids or a medium of the cell culture media type containing the nucleic acids, said medium being nondenaturing for the DNA and not saturated with calcium and phosphate; this medium causing epitaxial carbonated apatite growth at the surface of said powders and ceramics.

Regarding Claims 4-7, Troczynsky et al teach the production of calcium phosphate particles is carried out by means of a medium simulating the extracellular fluids or a medium of the cell culture media type (also called "simulated body fluid) containing the drug (i.e. DNA as disclosed as a gene therapy drug), said medium being nondenaturing for the DNA and not saturated with calcium and phosphate; this medium causing epitaxial carbonated apatite growth at the surface of said powders and ceramics (e.g. page 17, lines 8-12 and page 19, lines 9-11).

Claim 8 specifies within Claim 1 that steps (a) and (b) are carried out simultaneously or successively.

Regarding Claim 8, Troczynsky et al teach that steps (a) and (b) are carried out simultaneously or successively (e.g. page 10, lines 21-26; page 12, lines 21-23; page 13, lines 1-11).

Claim 9 is drawn to the method as claimed in claim 7 to attach DNA under physiological pH conditions to calcium phosphate particles.

Regarding Claim 9, Troczynsky et al teach the process of making the calcium phosphate (in particular hydroxyapatite) microspheres (particles) designed specifically for gene therapy through gene/DNA/plasmid delivery occurs at room-temperature (i.e. about 25°C) and teach the drug material (e.g. DNA) is exposed to water-based solution of sodium phosphate and placed in an incubator at 37°C, 100% relative humidity, for up to 24 h. (e.g. page 12, lines 21-23).

Claim 12 is drawn to a method of preparing a medicament for transfecting *in vivo* cells contained in a tissue or in an organ utilizing the particles obtained by the method as claimed in claim 1.

Regarding Claim 12, Troczynsky et al teach therapeutic hydroxyapatite coated microspheres for the delivery of DNA to cells in vivo, contained within an organism (e.g. contained in a tissue or in an organ) (e.g. see abstract, lines 1-11 and page 6, lines 27-30).

Claim 2 specifies within Claim 1 that the solution in step (a) and (b) comprises a 0.12 M phosphate buffer (pH 6.8).

However, Troczynsky et al differs from the instant invention because although they teach a phosphate buffer solution that is 0.25 M (page 16, lines 18-19 and page 18, lines 32-35) and a PBS solution that is pH 7.4 (page 17, Example 4, line 31) they fail to explicitly teach that a phosphate buffer solution of steps (a) and (b) comprises a 0.12 M phosphate buffer (pH 6.8) (e.g. instant Claim 2).

In addition, Troczynsky et al **fails to** explicitly teach that the type of DNA is plasmid DNA or that the DNA is explicitly attached to the particle "surface".

In the instant case, it would have been primafacie obvious to one of ordinary skill in the art at the time the invention was made to use plasmid DNA for the DNA attached to the particles to be plasmid DNA because plasmid DNA is the DNA form most often used for gene therapy and DNA transfection methods and is the form most often prepared in large preparations in the laboratory.

In addition, it would be primafacie obvious for the DNA to be attached to the particle surface since the claims do not explicitly require and outer or inner surface, the attachment of the DNA would inherently occur on a particle surface.

In addition, absent evidence to the contrary, it would have been primafacie obvious to use a phosphate buffer solution comprising a 0.12 M phosphate buffer (pH 6.8) in combination with the method of Troczynsky et al because et al because the substitution of one known element for another would have yielded predictable results to one of ordinary skill in the art at the time of the invention. One would have a reasonable expectation of success combining the teachings of the art because Troczynsky et al state that "we disclose hereby a new, safe and inexpensive way to deliver drugs, proteins, genes and antisense oligos in vivo" (page 7, lines 19-20) and the use of a phosphate buffer solution that is 0.12 M (pH 6.8) for the purposes of solutions containing DNA was routinely practiced at the time of the invention.

Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent evidence to the contrary, there would have been a reasonable expectation of success to result when utilizing a phosphate buffer solution that is 0.12 M (pH 6.8) in the method of Troczynsky et al.

In view of the foregoing, the method of claims 1-9 and 12, as a whole, would have been obvious to one of ordinary skill in the art at the time the invention was made. Therefore, the claims are properly rejected under 35 USC *§103(a)*.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to CATHERINE HIBBERT whose telephone number is (571)270-3053. The examiner can normally be reached on M-F 8AM-5PM, EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached on 571-272-0951. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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Examiner/AU1636

/ Christopher S. F. Low /
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